# Aseptic Meningitis associated with ECHO Virus Type 9 Infection

## With Special Reference to Variability by Sex and Incidence of Paralytic Sequelae

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■ *The clinical and clinical laboratory findings in a group of 104 patients with aseptic meningitis associated with ECHO-9 infection were widely variable.*

*A male to female case ratio of 3.7:1 was noted, and the mean age of the female group was significantly greater than that of the male group. The median of cerebrospinal fluid leukocyte counts was significantly higher in the male than in the female patients. Clinical manifestations of the disease were similar to those noted in other reports. Residual paralysis was rare and mild.*

*Further study of the ecology of aseptic meningitis seems indicated for elucidation of the factors governing variability of the disease by sex.*

IN 1954, ECHO-6 became the first ECHO virus unequivocally associated with aseptic meningitis.[2,5] During the following year, ECHO-9 was etiologically implicated in the same syndrome.[1,10] Since then, numerous reports describing the central nervous system symptoms, skin manifestations and epidemiologic features of ECHO-9 have appeared in the literature, including reports by Nihoul,[13] Sabin,[15] and Solomon[16] and their coworkers which gave detailed descriptions of epidemic outbreaks of ECHO-9 disease.

This report describes and analyzes the syndrome of aseptic meningitis as one of the clinical expressions of ECHO-9 infection as observed in 104 patients in Los Angeles County. The high male to female ratio often observed in studies of aseptic meningitis is analyzed and discussed in detail, as is the problem of residual muscle weakness associated with ECHO-9 infection.

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## Plan of Study

### *Selection of Patients*

All the patients included in this report had been referred to the Communicable Disease Service of the Los Angeles County General Hospital for diagnosis and treatment. Patients are accepted from the entire County, and all age and socioeconomic groups are represented.

All of the patients included in this report had signs of meningeal irritation (headache, stiff neck and/or stiff back, positive Kernig's or Brudzinski's signs) and cerebrospinal fluid pleocytosis greater than five cells per cubic millimeter. In none of them was there coma, disorientation, convulsions, abnormal or pathological reflexes or obvious flaccid paralysis. ECHO-9 infection was documented in each patient in one or more of the following ways: (1) Isolation of virus from the cerebrospinal fluid with or without a four-fold or greater rise in neutralizing antibody titer in the serum; (2) A four-fold or greater rise in serum neutralizing antibody titer with or without isolation of the virus from pharyngeal secretions or fecal specimens.

### *Clinical Studies*

Each patient had a routine hospital work-up including physical examination and appropriate clinical laboratory studies. In most patients a competent physical therapist did a detailed grading of muscle function at the time of discharge and again 60 to 120 days later.

### *Virus Laboratory Procedures*

Specimens for viral studies were obtained on admission and stored at −20°C for periods varying from 24 hours to one year until studied. At least one isolation specimen (cerebrospinal fluid, stool, rectal swab or throat swab) was available from every patient, and a minimum of three specimens were cultured from 98 of the 104 patients. All isolation attempts were made in monkey kidney tissue culture,* and all isolations were made on the first passage. Viral isolates were typed by tube neutralization tests utilizing hyperimmune rabbit sera.†

Infection with ECHO-9 was confirmed by a four-fold rise in antibody titer by the tube neutralization test. Whenever possible, a strain isolated from the patient was used because the prototype ECHO-9 virus seemed to vary antigenically from many of the strains isolated from this series of patients.

*Obtained from Microbiological Associates, Inc., Bethesda, Maryland, and The Tissue Culture Laboratory, Oakland, California.

†Obtained from Microbiological Associates, Inc., Bethesda, Maryland.

### *Statistical Methods*

Measures of central tendency and dispersion were calculated according to standard methods.[3a] Student's t test was employed to test the significance of differences between two means in Tables 1 and 5.[3b] The medians in Tables 3, 4 and 6 were compared by the non-parametric median test for two samples utilizing $\chi^2$, based upon a four-fold contingency table, and corrected for continuity.[12]

## Epidemiological Observations

### *Temporal and Etiologic Description*

Patients with ECHO-9 aseptic meningitis were observed during the fall of 1961 (17 cases) and during every month of 1962 (87 cases) except January, February and March. The peak incidence of the disease occurred during August and September, 1962. No geographic localization of ECHO-9 cases in the County was detected.

During 1962, the only complete year for which both virus laboratory and reporting data are available, 532 cases of aseptic meningitis were reported in Los Angeles County; 395 (74 per cent) of the patients were admitted to Los Angeles County General Hospital and all were studied by our laboratory. ECHO-9 infection was well-documented in 87 of the cases detected in 1962. These 87 patients constituted 16 per cent of the total number with aseptic meningitis reported in the County and 22 per cent of those admitted. An additional 28 patients with onset of illness in 1962 were not included in the present report because isolation of ECHO-9 from throat swabs, rectal swabs or stools was not accompanied by significant rises in neutralizing antibody titers.

Documentation of ECHO-9 infection was accompanied by virus isolation from one or more sites in 100 of the 104 patients in the study group. The virus was recovered from the cerebrospinal fluid in 57 instances. Fifty-four of these 57 patients had adequate paired serum specimens for neutralization tests, and in 13 of these 54 a four-fold or greater rise in neutralizing antibody titer did not develop. ECHO-9 virus was isolated from pharyngeal secretions and/or stool with an accompanying four-fold or greater rise in neutralizing antibody titer in 43 of the remaining 47 patients. Four patients with four-fold or greater titer rises without isolates were included.

As ECHO-9 serologic study had not been completed at the time of this report in those cases of aseptic meningitis without isolates, the final total of proven ECHO-9 infections in 1962 will undoubtedly be higher. It should be emphasized that the number of cases of aseptic meningitis reported in Los An-

geles County during the study period was not unusual, and in this sense, at least, ECHO-9 disease was not epidemic. Due to a lack of virologic data in earlier years, we are unable to state with certainty that ECHO-9 caused an unusually high proportion of the cases of aseptic meningitis in 1961-62; however, in 1963 a much smaller proportion of the cases of aseptic meningitis observed at Los Angeles County General Hospital was caused by ECHO-9.

During the period of this study, the following agents were also associated with aseptic meningitis: Mumps; ECHO viruses types 2, 5, 6, 14, 15, and 21; Group A, Coxsackie type 9; Group B, Coxsackie types 2 and 5; poliovirus type 1; and *Herpesvirus hominis.*

### *Characteristics of the Study Group*

The age and sex distribution of the patients studied is shown in Table 1. Of the 104 patients, 82 (79 per cent) were males and 22 (21 per cent) were females. The ratio of males to females was highest between ages 0-4, approaching unity after age 20. The male age range was 0.6 to 37 years and the female range 2 to 54 years, while the mean age was 19.1 years for females and 12.8 years for males. From these data (Table 1), it would appear that the average age of the females was significantly greater ($p<.05$) than that of the males.

Negroes constituted 22 per cent of the study group, while the remainder was Caucasian. No significant differences were noted between racial groups in any of the disease manifestations studied.

Seven families with multiple cases were studied. Six families with two cases each and one family with four were seen, a total of 16 cases. With one exception, the secondary cases in families occurred within ten days of the primary case; in the exception the interval was two months.

## Clinical Observations

Taking the day of the first symptoms as the first day of disease, the mean duration of disease at the time of admission was 3.9 days with a range of 1 to 11 days. The typical onset was abrupt and almost always accompanied by fever. Headache was an almost invariable complaint except by patients under four years of age. Nuchal rigidity was noted in 80 cases (77 per cent) either by the patient's family physician or the admitting resident. In the remaining 24 cases, lumbar puncture was prompted by an unexplained febrile illness often coupled with a history of family or other close contact with a case of "meningitis."

The average duration of disease, measured from date of onset to date of discharge, was 8.9 days with a range of 4 to 21 days. These two statistics of length of illness also did not vary significantly between the sexes.

TABLE 1.—*Age and Sex Distribution*

| *Age in Years* | *Sex Distribution* | | |
|---|---|---|---|
| | *Males* | *Females* | *Total* |
| 0- 4 | 12 | 1 | 13 |
| 5- 9 | 24 | 5 | 29 |
| 10-14 | 23 | 5 | 28 |
| 15-19 | 7 | 0 | 7 |
| 20-29 | 11 | 8 | 19 |
| 30+ | 5 | 3 | 8 |
| Total | 82 | 22 | 104 |
| Mean age (years) | 12.82 | 19.14 | 13.7 |
| Standard deviation | 9.28 | 13.01 | 10.23 |
| Range (years) | 0.6-37 | 2-54 | 0.6-54 |

### *Fever*

A biphasic illness was noted in 11 (11 per cent) of the patients. That is, they had an initial acute, non-specific, febrile illness followed by a 24 to 72-hour period of well-being before the onset of the symptoms prompting admission to the hospital. As most of the biphasic courses were recorded in the younger patients, it was difficult to be certain whether the illnesses were truly biphasic or were two separate illnesses.

The mean temperature (rectal) on admission to the hospital was 101.3°F with a range of 98.2 to 104.4°F. Twenty-three patients were afebrile (less than 100°F) on admission, but in 18 of these temperature in excess of 100°F developed later. Five gave no history of fever before admission and remained afebrile throughout the hospital course. The mean duration of fever after hospitalization was 3.8 days with a range of 0 to 8 days. The duration of fever did not vary significantly between the two sexes.

### *Rash*

An exanthem was observed in 13 (12.5 per cent) of the 104 patients. These 13 patients ranged in age from seven months to 37 years. However, 11 of the 13 were less than 15 years of age, and eight of the 11 were five years of age or younger. Two of the 13 were females, a ratio not differing materially from the ratio of females to males in the total group. The rash varied in appearance from macular to maculopapular to petechial to combinations of the three characteristics.

A petechial rash without associated macules was present in three patients, aged 1, 2 and 3 years. The eruption was limited to the face and neck in one case and extended down over the thoraces in the other two. The latter two cases simulated meningococcal disease and received antibiotic treatment initially. In a fourth patient, the exanthem

was diagnosed initially as roseola. In another the initial impression was rubella because of the presence of posterior cervical adenopathy; however, the rash was limited to the buttocks and lower abdomen. Among the other eight patients with rash, the eruption was generalized in three cases, involved the chest, face and neck in three, was limited to the extremities in one, and limited to the chest in another.

### *Conjunctivitis and Photophobia*

Only one patient, a 31-year-old man, manifested objective conjunctivitis. The condition lasted two days and was mild, bilateral, non-purulent and accompanied by photophobia.

Six of the 62 patients (ten per cent) who were ten years old or older, complained of photophobia accompanied by headache. The absence of these complaints among the younger children may reflect communication problems rather than true absence of the symptoms.

### *Respiratory Symptoms*

Only four patients, aged 5, 15, 37 and 54 years, complained of sore throat before admission and none of these had objective evidence of pharyngitis when first examined. In eight additional patients there was objective evidence of non-exudative pharyngitis or pharyngotonsillitis. These eight ranged in age from 2 to 40 years with only two under the age of six. Throat cultures for beta hemolytic streptococci were negative in all eight cases.

Only three patients had lower respiratory tract symptoms. One, aged ten years, had cough as well as upper respiratory tract symptoms. A second, aged ten years, had bronchitis. The third patient in this group complained of cough and sore throat.

Unilateral catarrhal otitis media was present in one infant, and prodromal symptoms of an upper respiratory illness with cough were seen in two other children.

### *Gastrointestinal Symptoms*

Forty-eight (46 per cent) of the patients reported vomiting before admission. Although nausea and vomiting were the most common complaints referable to the gastrointestinal tract, a few patients complained of abdominal pain.

### *Genito-urinary*

One patient, a 14-year-old white male, experienced urinary retention of one day's duration. He did not require catheterization. None of the other patients had symptoms or abnormal laboratory findings referable to the urinary tract.

### *Neurological Symptoms*

Three patients, aged 14, 15 and 45 years, complained of "dizziness." This symptom was of short duration and resolved completely in all three. One patient, a 21-year-old white woman, complained of blurred vision and headache. These symptoms were also of short duration and resolved spontaneously.

### *Adenopathy*

Lymphadenopathy was detected in only two patients. The illness in one of these patients was diagnosed initially as rubella. The other patient was a 3-year-old white boy with cervical and inguinal adenopathy. ECHO-9 virus was isolated from a specimen of cerebrospinal fluid obtained on admission. After a stormy febrile course, the aseptic meningitis resolved, but the lymphadenopathy had only partially subsided at the time of discharge.

### *Muscle Function Evaluations*

Detailed muscle function evaluations were performed on 94 (90 per cent) of the patients just before discharge, and 62 (60 per cent) were reevaluated 60 or more days later. The results of these evaluations, with each patient tabulated by the rating of his weakest muscle group, are recorded in Table 2.

Eighty-eight (85 per cent) of the patients received grades of "normal" (N) or "good" (G) on primary evaluation. All but one of the patients with G scores had apparent weakness limited to the flexors of the neck or trunk or both. In addition to trunk and neck flexor weakness, one 15-year-old boy received G scores for all the muscle groups of his left shoulder and elbow on primary grading, and then received N scores on reexamination 62 days later.

TABLE 2.—*Muscle Function Evaluations (Score of Weakest Muscle Group)*

| | *Immediately Before Discharge* | | *60+ Days After Discharge* | |
|---|---|---|---|---|
| | *No.* | *Per Cent* | *No.* | *Per Cent* |
| Normal | 54 | 51 | 38 | 37 |
| Good | 34 | 33 | 21 | 20 |
| Fair | 1 | 1 | 2 | 2 |
| Not done | 10 | 10 | 42 | 40 |
| Not valid* | 5 | 5 | 1 | 1 |
| Total | 104 | 100 | 104 | 100 |

* Patients too young for reliable grading.

Normal: Complete range of motion against gravity with full resistance.

Good: Complete range of motion against gravity with some resistance.

Fair: Complete range of motion against gravity.

Poor: Complete range of motion with gravity eliminated.

Trace: Evidence of slight contractility. No joint motion.

Zero: No evidence of contractility.

The one "fair" (F) score noted on primary grading resulted from weak trunk flexors, but this patient was not available for follow-up testing.

Scores of N or G were recorded in 59 instances 60 or more days after discharge. Forty-two patients (40 per cent) did not appear for this evaluation, and muscle function of one infant patient could not be adequately evaluated because of lack of cooperation. All of the ten patients who received G scores on both examinations, and six of the eight whose scores went from N to G, had weakness limited to the neck flexors, the trunk flexors or both. Two other patients with initial N scores had G ratings on reevaluation. One, a 12-year-old boy, received a G score on his right wrist extensors 66 days after discharge, and the other, a 13-year-old boy, had bilateral weakness of the hip abductors.

Two patients received F scores on long-term muscle function evaluation. A 6-year-old girl had an F score on the function of the internal and external rotators of her right shoulder 69 days after the onset of illness, but unfortunately an earlier muscle function evaluation was not available for this patient. The second patient, a 21-year-old woman, had a completely normal rating on discharge, but stiffness and limitation of motion of trunk and hip flexors four months later resulted in an F score.

One 21-year-old woman, who had an N score at the time of discharge, complained of left lower extremity weakness and easy fatigability 84 days after the onset of illness, but no weak muscle groups were detected upon examination.

None of the patients had pronounced disability on any muscle function examination, and none had detectable muscular atrophy. Indeed most of the G ratings and one of the three F scores were due to apparent weakness of neck and trunk flexors which might have been caused by residual meningeal irritation. This leaves one patient in 89 who had definite muscular weakness on primary grading in muscle groups other than neck or trunk flexors, and four of 61 (6 per cent) with deficits in muscle groups other than neck or trunk flexors on evaluation 60 or more days after discharge. If only F scores for muscle groups other than trunk and neck flexors are considered, none of 59 had significant weakness on primary grading, and two of 61 (three per cent) 60 or more days later.

TABLE 3.—*Leukocyte Counts in Cerebrospinal Fluid in 104 Patients, 82 Male, 22 Female*

| | *Leukocytes per cu mm* | | |
|---|---|---|---|
| | *Males* | *Females* | *Total* |
| Mean | 618 | 322 | 553 |
| Median | 450 | 160 | 305 |
| Range | 9 to 2300 | 23 to 1600 | 9 to 2300 |

## Clinical Laboratory Data

The specimens yielding the clinical laboratory data to be presented in this section were taken at or a few hours after admission. Only data from the same specimen (for cerebrospinal fluid) or those taken at the same time (blood) were tabulated. Measurements of central tendency and dispersion of cerebrospinal fluid cell counts are presented in Table 3. As the cell counts did not approximate a normal distribution, medians were utilized in the statistical comparisons. The median cell count of the male group was significantly greater ($p<.05$) than that of the female group. As the mean duration of disease at the time the spinal fluid specimens were obtained was 4.15 days for males and 3.73 for females, an insignificant difference, this difference in cell counts could not be attributed to variation in the time of sampling.

Table 4 shows spinal fluid cell differential counts. All the cells counted were mononuclear or polymorphonuclear. The wide range of proportions of mononuclear cells should be noted. Here again, since the distribution of the differential counts did not approximate normal, medians were compared statistically. There was no significant difference in the median per cent mononuclears between the male and female groups.

Cerebrospinal fluid protein levels may be seen in Table 5. Like the cell counts and cell type differentials, the values had wide ranges. As the protein levels approximated normal distributions, mean cerebrospinal fluid protein levels were compared for the male and female groups and did not vary significantly by sex.

Leukocyte counts in specimens of peripheral blood varied widely (Table 6) and were not nor-

TABLE 4.—*Cerebrospinal Fluid Cell Differential Counts in 103 Patients,* 81 Male, 22 Female*

| | *Per Cent Mononuclear Cells* | | |
|---|---|---|---|
| | *Male* | *Female* | *Total* |
| Mean | 79 | 88 | 81.1 |
| Standard deviation | 22.2 | 15.9 | 21.1 |
| Median | 90 | 91 | 90 |
| Range | 16 to 100 | 41 to 100 | 16 to 100 |

*Differential not done on one patient.

TABLE 5.—*Cerebrospinal Fluid Protein Levels (mg per 100 ml) in 93 Patients,† 73 Male, 20 Female*

| | *Protein mg per 100 ml* | | |
|---|---|---|---|
| | *Male* | *Female* | *Total* |
| Mean | 51.7 | 55.8 | 52.5 |
| Standard deviation | 22.8 | 27.0 | 23.4 |
| Range | 14 to 109 | 20 to 122 | 14 to 122 |

†Not performed on 11 specimens.

TABLE 6.—*Leukocyte Counts in Peripheral Blood in 99 Patients,* 79 Male, 20 Female*

| | *Leukocytes per cu mm* | | |
|---|---|---|---|
| | *Male* | *Female* | *Total* |
| Mean | 9,290 | 9,510 | 9,334 |
| Median | 8,900 | 8,700 | 8,900 |
| Range | 3,500 to 25,000 | 4,000 to 15,000 | 3,500 to 25,000 |

*Count not performed on day of cerebrospinal fluid specimen in five instances.

mally distributed. Median counts did not vary significantly between the two sexes. The percentage of neutrophils ranged from 25 to 94 per cent, but most differential counts were within normal limits. The clinical laboratory findings in relation to the ability to culture ECHO-9 from cerebrospinal fluid have been described in detail in another publication.[14]

## Discussion

In spite of the increased depth of study made possible by modern virologic methods, there is no good explanation for the male to female ratio of 3.7:1 observed in this study, and the equally high ratios noted in other studies of aseptic meningitis.[4,6,15,16] As the preponderance of males was more pronounced in the lower age ranges, the male to female case ratio must be interpreted as a variable dependent on age. Unfortunately, age-matched comparisons by sex, of the disease attributes that were investigated in this study, could not be done because of the small numbers of females in each age group.

The severity of illness as measured by duration of fever and total length of illness did not vary significantly by sex. Males were not admitted significantly earlier in the course of their illnesses. In short, the male group was not "sicker" than the female group. Of course, the study group consisted only of patients with clinically evident ECHO-9 aseptic meningitis, and ECHO-9 infection may be subclinical or result in non-specific minor illness: also, good estimates of age-specific and sex-specific attack rates for subclinical or minor infection in the community are not available. Assuming that exposure to infection were equal for both sexes, the preponderance of males with ECHO-9 aseptic meningitis could be explained either on the basis of a higher rate of absolute resistance to infection in females or a greater rate of relative resistance resulting in more subclinical infections or minor illnesses. In the male group, the higher median white cell count in cerebrospinal fluid is suggestive of real differences by sex in the response to clinically manifest ECHO-9 aseptic meningitis. More complete ecological studies are needed to clarify the precise mechanisms of these sex-dependent differences.

Except for the greater frequency of rash in the present study group, the clinical syndromes observed were indistinguishable from those noted in the large series of cases of aseptic meningitis caused by various enteroviruses reported by Meyer and coworkers[11] and Lepow and coworkers.[7] Although ECHO-9 is the enterovirus most commonly associated with rash, it is not unique in this respect. Rash has been reported in association with aseptic meningitis due to ECHO-6,[4] Group A, type 9, Coxsackie[7,8] and others.[17]

There were few outstanding differences among the major clinical findings in the present study group and similar groups of patients with ECHO-9 aseptic meningitis reported by Sabin[15] and Solomon[16] and their coworkers. The proportion of patients manifesting abdominal pain, photophobia, headache, stiff neck and fever was similar in all three studies. Vomiting occurred in about 50 per cent of the patients in the present study group and in 77 per cent of the patients reported by Solomon and coworkers.[16] The higher average age in the present study group probably accounts for this discrepancy. Sabin and coworkers reported vomiting in 50 per cent of their patients, with a higher incidence in the younger age group. The 13 per cent incidence of rash noted in the present study is not significantly different from the 20 per cent incidence reported by Sabin[15] but it differed significantly ($p<.05$) from the 28 per cent noted by Solomon.[16] The 11 per cent rate of biphasic illness observed differed significantly from the 25 per cent rate reported by Sabin[15] ($p<.05$), but was not significantly different from the 17 per cent reported by Solomon.[16]

Respiratory symptoms and signs were infrequent in the present series. Pharyngitis was an objective finding in only 7.7 per cent of the patients. Sabin and coworkers[15] noted this finding in 55 to 82 per cent of the patients they observed, with a higher incidence in the younger age group, while Solomon and coworkers[16] noted objective pharyngitis in 39 per cent of patients. Again the discrepancy may have been a function of the younger average age of the patients in the other two studies. Symptoms of lower respiratory tract disease were uncommon (4 per cent) in the patients in our series, while Solomon and coworkers[16] noted cough in 16 per cent. As symptoms referable to irritation of the respiratory tract may have other cause than microbial infection, these differences may be fortuitous. However, the ECHO group has been definitely associated with respiratory tract disease, so respiratory tract symptoms due to ECHO-9 would not be unexpected.

The low frequency of residual weakness observed in the present series is similar to the experience of other investigators, but it has been variable in our experience.[18] Although variations in the skill and patience of the examiner are probably important, particularly in young children, evaluation of muscle function is a comparatively well-standardized art.[9] Differences in the rates of F or lower muscle function scores in different series of patients with aseptic meningitis due to ECHO-9 or other agents are almost certainly real, and probably reflect intratypic strain variations in neuropathogenicity.

The extreme variation in leukocyte counts and cell differentials in peripheral blood noted in this study has been observed previously[15,16] and is not peculiar to aseptic meningitis caused by ECHO-9. Karzon and coworkers[4] reported counts ranging from "less than 5,000 to more than 17,000 per cubic mm" in the same syndrome due to ECHO-6. It is interesting to note that polymorphonuclear leukocytes were the predominant cells in the peripheral blood, while mononuclear cells predominated in the cerebrospinal fluid. These data merely emphasize the variability of individual cases, and the fact that classical descriptions of leukocyte counts (in peripheral blood and cerebrospinal fluid) in viral infections are based on many cases caused by different agents and may need to be more specific.

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